

The opinion in support of the decision being entered today  
is *not* binding precedent of the Board.

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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*Ex parte JULJA BURCHARD*

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Appeal 2007-3267  
Application 09/616,849  
Technology Center 1600

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Decided: September 28, 2007

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Before TONI R. SCHEINER, DONALD E. ADAMS, and ERIC GRIMES,  
*Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

**DECISION ON APPEAL**

This is an appeal under 35 U.S.C. § 134 involving claims to a method for evaluating the binding properties of a polynucleotide probe. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

**BACKGROUND**

“Oligonucleotide sequences are particularly useful as probes on microarrays and in other applications that involve nucleic acid hybridization.

. . . However, because of their small size, oligonucleotide probes frequently correspond to genomic sequences that are non-unique and, as a result, may hybridize to more than one polynucleotide sequence in a sample” (Specification 2). This lack of specificity can yield false positive measurements (*id.*).

“Conversely, an oligonucleotide probe may also hybridize to a target polynucleotide sequence of interest more weakly than predicted, e.g., from predicted hybridization binding energies. Such probes can result in false negative hybridization measurements, reflecting a lack of sensitivity” (*id.*).

The Specification discloses methods of evaluating “both the sensitivity and the specificity with which a probe binds to a particular target” (*id.* at 4). This evaluation is accomplished by “comparing the amount or number of molecules in a first sample that bind to molecules of a probe to the amount or number of molecules in a second sample that bind to molecules of the same probe” (*id.*).

The first sample, “referred to . . . as a ‘specific binding sample,’ preferably comprises molecules of a particular target that is generally a target of interest to a user” (*id.*). The second sample, “referred to . . . as a ‘non-specific binding sample,’ comprises molecules of a plurality of different (i.e., non-identical) targets other than the particular target of interest” (*id.*).

## DISCUSSION

### 1. CLAIMS

Claims 27, 29, 30, 33-40, 42-54, 59-67, 73-75, 84, 85, and 90-104 are pending and on appeal. Claim 27 is representative and reads as follows:

27. A method for evaluating a binding property of a polynucleotide probe to a target nucleotide sequence, said polynucleotide probe comprising a predetermined nucleotide base sequence that is complementary to at least a hybridizable portion of said target nucleotide sequence, said method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe and the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, wherein:

- (a) the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and
- (b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence, and wherein said ratio is used as a measure of said binding property, thereby evaluating said binding property of said polynucleotide probe.

Thus, claim 27 is directed to a method of evaluating the binding properties of a polynucleotide probe having a predetermined sequence. A ratio is obtained by comparing the hybridization of a first sample, in which at least 75% of the polynucleotides comprise the target sequence, to the hybridization of a second sample, in which the polynucleotides all have different sequences. The ratio determined from the amount of hybridization in the two samples is used as a measure of the binding of the probe to its target sequence.

## 2. PRIOR ART

The Examiner relies on the following references:

Lo US 4,900,659 Feb. 13, 1990  
David J. Lockhart et al., *Expression monitoring by hybridization to high-density oligonucleotide arrays*, 14 Nature Biotechnology 1675-1680 (December 1996) (“Lockhart Article”).

Lockhart US 6,344,316 B1 Feb. 5, 2002  
 (“Lockhart Patent”)

## 3. OBVIOUSNESS-- LO AND THE LOCKHART ARTICLE

Claims 27, 29, 30, 33-40, 42-54, 59, 60, 64, 65, 67, 73, and 90-104 stand rejected under 35 U.S.C. § 103 as obvious in view of Lo and the Lockhart Article (Answer 2-11).

The Examiner cites Lo as disclosing a method for evaluating a polynucleotide probe by determining the ratio of the amount hybridization of the probe to first and second polynucleotide samples (*id.* at 3). The Examiner states that the first sample “comprises a plurality of molecules comprising the target chromosomal DNA e.g. strain 53414 . . . and the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis* . . . and chromosomal DNA from *N. gonorrhoeae* . . .)” (*id.*, citation omitted).

The Examiner concedes that Lo does not “specifically teach [that] the probes have a predetermined base sequence” (*id.*). To meet that limitation, the Examiner cites the Lockhart Article as teaching a similar probe evaluation method in which target polynucleotides are hybridized to probes having sequences that are “predetermined and complementary to at least a part of the target (i.e. from 600 bases of the 3’ end of translated region of

RNA/specific cytokine RNA) and comparing the hybridization to a second sample comprising a plurality of different polynucleotides i.e. complex RNA population (page 1680, left column)” (*id.*).

The Examiner concludes that one of ordinary skill would have considered it obvious “to apply known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected benefit of obtaining useful probes based on the growing body of sequence information for simultaneous monitoring tens of thousands of genes as taught by Lockhart” (*id.* at 4).

Appellant argues that Lo does not “teach or suggest the desirability of using or determining the sequences of its target and/or probes. Instead, its method steps are chosen such that probes can be obtained from the chromosomal DNA of *N. gonorrhoeae* without knowledge of either the target sequence or the probe sequences” (Br. 12). Therefore, Appellant concludes, “neither Lo [n]or the Lockhart Article provides any motivation to a person skilled in the art for the combination. A person skilled in the art would not be motivated to use sequence information in Lo’s method” (*id.* at 13).

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. “[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.”

*In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (citations omitted, bracketed material in original). Thus, “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be

some articulated reasoning *with some rational underpinning* to support the legal conclusion of obviousness.” *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added).

We agree with Appellant that the Examiner has not established a *prima facie* case of obviousness based on the asserted combination of references. The only reason asserted by the Examiner that one of ordinary skill would have combined the Lockhart Article with Lo is to apply “known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected benefit of obtaining useful probes based on the growing body of sequence information for simultaneous monitoring tens of thousands of genes as taught by Lockhart (Abstract)” (Answer 4; *see also* 13-14). Thus, the Examiner’s sole basis for combining the two cited references is the following statement in the abstract of the Lockhart Article:

This approach provides a way to use directly the growing body of sequence information for highly parallel experimental investigations. Because of the combinatorial nature of the chemistry and the ability to synthesize small arrays containing hundreds of thousands of specifically chosen oligonucleotides, the method is readily scalable to the simultaneous monitoring of tens of thousands of genes.

(Lockhart Article 1675 (abstract)).

We are not persuaded by the Examiner’s reasoning. The Lockhart Article discloses “a method for the simultaneous monitoring of the expression levels of many genes in parallel” by determining “the relative concentrations of mRNAs based on hybridization of entire mRNA

populations to high-density arrays of synthetic oligonucleotides" (*id.* at 1675, left hand column).

Thus, when the abstract of the Lockhart Article discusses the advantages of "highly parallel experimental investigations" and "simultaneous monitoring of tens of thousands of genes," that discussion is in reference to the array-based technique's capacity to simultaneously monitor cellular concentrations of many different mRNA species, not in the context of how the oligonucleotide probe is generated. Because the Lockhart Article's discussion of the advantages of its technique does not relate to probe evaluation, we do not agree with the Examiner that the advantages discussed by the Lockhart Article would have led one of ordinary skill to modify Lo's methods.

In contrast to the Lockhart Article, Lo does not disclose methods for analyzing gene expression patterns but for detecting *Neisseria gonorrhoeae* (Lo, abstract). Lo teaches that *N. gonorrhoeae* and *Neisseria meningitidis* are difficult to distinguish in hybridization assays because their chromosomal DNAs are highly homologous (*id.* at col. 2, l. 37, through col. 3, l. 30). Lo addresses this problem by obtaining probes from *N. gonorrhoeae* chromosomal DNA via restriction enzyme digestion, and then testing the probes for their ability to distinguish between *N. gonorrhoeae* sequences and *N. meningitidis* sequences (*id.* at cols. 5 through 12).

The Examiner does not point to, and we do not see, any teachings in either of the cited references, or any reason derived from the knowledge of those skilled in the art, suggesting that one of ordinary skill using Lo's methods to prepare probes specific for *N. gonorrhoeae* would have

considered it desirable to generate probes capable of monitoring tens of thousands of genes as taught in the Lockhart Article.

We note the Lockhart Article's disclosure that the oligonucleotide probes were selected by hybridizing an array of probes to a first set of target sequences complementary to the probe sequences ("specific cytokine RNAs"), and also by hybridizing the same array to a second "complex RNA population that did not contain the cytokine RNAs" (Lockhart Article 1680, left hand column). The Lockhart Article states that "[t]hese two types of experiments were used to determine which probes hybridized strongly and specifically, and which ones were poor or promiscuous hybridizers" (*id.*).

Thus, the Lockhart Article's method of determining probe suitability for the expression analysis has steps very similar to the probe evaluations (a) and (b) in Appellant's claim 27. Again, however, the Examiner has not explained why one of ordinary skill would have applied those screening methods, directed to generating many thousands of oligonucleotide probes for gene expression analysis, to Lo's methods, in which the probes need only be capable of distinguishing between *N. gonorrhoeae* and *N. meningitidis*.

We agree with Appellant that the rationale advanced by the Examiner for combining the references does not support a *prima facie* case of obviousness. We therefore reverse the Examiner's rejection of claims 27, 29, 30, 33-40, 42-54, 59, 60, 64, 65, 67, 73, and 90-104 under 35 U.S.C. § 103 as obvious in view of Lo and the Lockhart Article.

#### 4. OBVIOUSNESS -- LO, THE LOCKHART ARTICLE, AND THE LOCKHART PATENT

Claims 61-63, 66, 74, 75, 84, and 85 stand rejected under 35 U.S.C. § 103 as obvious in view of Lo, the Lockhart Article, and the Lockhart Patent (Answer 11-13). Claims 61-63, 66, 74, 75, 84, and 85 ultimately

depend on claim 27, discussed above, or claim 67, which recites a process similar to that of claim 27. The Examiner relies on Lo and the Lockhart Article for the limitations of claims 27 and 67, and cites the Lockhart Patent to meet the limitations of the dependent claims (Answer 11-13).

We reverse this rejection as well. As discussed above, we do not agree with the Examiner that one of ordinary skill using Lo's methods to prepare probes capable of distinguishing between *N. gonorrhoeae* and *N. meningitidis* would have considered it desirable to generate probes capable of monitoring tens of thousands of genes as taught in the Lockhart Article.

The Lockhart Patent is essentially a more detailed disclosure of the methods described in the Lockhart Article. In reviewing the Lockhart Patent, we do not see any disclosure that leads us to conclude that one of ordinary skill would have applied the teachings in the Lockhart Patent to Lo's methods. Nor do we see any disclosure in the Lockhart Patent that remedies the deficiency in the Examiner's primary combination of Lo and the Lockhart Article. We therefore reverse the Examiner's rejection of claims 61-63, 66, 74, 75, 84, and 85 under 35 U.S.C. § 103 as obvious over Lo, the Lockhart Article, and the Lockhart Patent.

#### OTHER ISSUES

In our view, the Lockhart Patent is the most relevant reference to the instantly claimed method. The Lockhart Patent discloses methods very similar to those of the instant claims for evaluating probes for use in the expression analysis methods. Specifically, the Lockhart Patent prepares a high density array of oligonucleotide probes which are "then hybridized with their target nucleic acid alone" (Lockhart Patent at col. 36, ll. 33-34; *see also*

col. 37, ll. 1-5). The Lockhart Patent's first hybridization step thus appears to correspond, for example, to hybridization (a) of instant claim 27.

The Lockhart Patent discloses that, after the first hybridization, the arrayed probes are "then hybridized with a high complexity, high concentration nucleic acid sample that does not contain the targets complementary to the probes" (*id.* at col. 36, ll. 34-37). The Lockhart Patent's second hybridization thus appears very similar to hybridization (b) of Appellant's claim 27.

The Lockhart Patent states that "[t]hose probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample are preferred probes for use in the high density arrays of this invention" (*id.* at col. 36, ll. 44-47). Thus, the Lockhart Patent compares data from essentially the same two experiments as hybridizations (a) and (b) in Appellant's claim 27, and therefore appears to disclose a determination of the same ratio recited in claim 27, as well as the use of that ratio in evaluating probes.

The Lockhart Patent appears to differ from claim 27 in that the high complexity sample used in the second hybridization does not necessarily contain polynucleotides that are all different from each other, as recited in claim 27's hybridization (b). However, it may be that one of ordinary skill in the art would have considered the method of claim 27 obvious from the Lockhart Patent despite this difference. On return of this case, we recommend that the Examiner consider whether the instant claims would have been obvious to those of ordinary skill in the art based on the Lockhart Patent, alone or in combination with other prior art.

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## SUMMARY

We reverse the Examiner's rejection of claims 27, 29, 30, 33-40, 42-54, 59, 60, 64, 65, 67, 73, and 90-104 under 35 U.S.C. § 103 as obvious over Lo and the Lockhart Article.

We also reverse the Examiner's rejection of claims 61-63, 66, 74, 75, 84, and 85 under 35 U.S.C. § 103 as obvious over Lo, the Lockhart Article, and the Lockhart Patent.

## REVERSED

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